

## Remarks

### I. Discussion of the Amendments

The specification is amended at p. 35, lines 1-8 to follow the expression "Alexa<sup>TM</sup> probes" with "a sulfonated aminocoumarin" and "a sulfonated rhodamine" that adequately describe these materials, as evidenced by the manufacturer's publication, R. P. Haugland et al. J. of Histochem. & Cytochem. (1999) 47(9): 1179-1188,<sup>1</sup> available well prior to the international filing date and the filing dates of the priority documents of the present application. Applicants have attached this publication to the present response as an evidentiary document for the Examiner's consideration. The Examiner's attention is directed specifically to p. 1180, left-hand column, 2nd full para. and p. 1182, Figure 1.

Prior to the entry of the present amendment, claims 2-40, 42-102, and 106-111 were pending, but claims 4-6, 13-16, 21-23, 27-31, and 43-102 were withdrawn from consideration.

Upon entry of the amendment, claims 6, 11, 22-23, 34-36, 106-107, and 109-111 are canceled without prejudice or disclaimer. Claims 2-5, 7-10, 12-21, 24-33, 37-40, 42-102, and 108 are now pending. Of these claims, claims 4-5, 13-16, 21-23, 27-31, and 43-102 remain withdrawn from consideration.

Claim 32, the only independent claim, is currently amended in order to improve readability and to incorporate the limitation found in previously presented claim 110. Support for amended claim 32 is found in previously presented claims 32, 110 and throughout the specification, e.g., see page 18, lines 29-34 and page 19, lines 25-30. Elected claims 2-3, 9, 19-20, 24-26, 40, and 108 are amended in order to improve readability without intention to alter their scope. Elected claim 42 is amended to include language from the specification at page 18, lines 30-32. Elected claim 19 is amended to remove the trademark expression "Alexa<sup>TM</sup> probes." Non-elected claims 4-6, 21, 27, 29-31, 43, 49, 52, 66-76, 79, 83, 85-86, and 93 are amended in order to improve readability.

No new matter is believed to be added upon entry of the amendment.

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<sup>1</sup> R. P. Haugland is the founder of Molecular Probes, Inc.

## **II. Interview Summary**

Applicants thank Examiner Steele for conducting the kind and courteous interview with Applicants' representatives, Adda Gogoris and Dan Evans, on November 2, 2010. The Applicants have not yet received an Interview Summary. During the discussion, Applicants offered to amend claim 32 as presently amended and directed the Examiner's attention to the specification for support for the amendment. During the discussion, Applicants' representatives explained that the number of particles (3 to 10) attached to each bead is important. This small number of particles permits each bead to be individually detectable by virtue of the spatial configuration of the particles in each bead and avoids the particles eclipsing one another, making the position of some particles undetectable and therefore useless in a spatial identification context. The Examiner expressed the concern that the carrier particles of Trau bearing reporter beads may still be within the claims, broadly interpreted, even after this amendment. This concern is addressed in the present response. Prior to the interview, the Examiner directed Applicants representatives' attention to the following U.S. patents: US 7,037,729; US 6,544,732; US 6,207,392; US 6,139,626; and U.S. 6,759,235. Although the pending claims have not been rejected in view of these new references, the Applicants believe that the composition of claim 32 is novel and unobvious over these additional references, on at least the same grounds as the references already applied to reject the claims.

## **III. Outstanding Rejections**

### **1) 35 U.S.C. § 112, first paragraph**

The rejection of claims 106-111 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is traversed (in part) and rendered moot (in part).

The rejection of claims 107 and 109-111 is rendered moot because claims 106-107 and 109-111 are now canceled without prejudice or disclaimer.

The rejection of claim 108 is traversed because adequate support for this claim is found throughout the specification. See for instance p. 1, lines 18-20, p. 15, lines 17-19, and p. 46, line 23 – p. 47, line 27 and especially Example 1 at p. 58, lines 1-19.

## **2) 35 U.S.C. § 112, second paragraph**

The rejection of claim 19 under 35 U.S.C. § 112, second paragraph is believed to be obviated by the amendment of that claim.

As noted above, the specification has been amended to provide language of what one of ordinary skill would know about "Alexa™ probes" as evidenced by the manufacturer's publication, R. P. Haugland et al. J. of Histochem. & Cytochem. (1999) 47(9): 1179-1188, attached for the Examiner's consideration. Claim 19 has been amended to replace "Alexa™ probes" to read: "a sulfonated aminocoumarin, a sulfonated rhodamine." Based on this amendment, it is believed that this rejection has been obviated. Withdrawal of this rejection is respectfully requested.

## **3) 35 U.S.C. § 102(b)**

The rejection of claims 2, 3, 7-12, 17-20, 24-26, 32, 38-40, 42, and 106-111 under 35 U.S.C. § 102(b) WO 99/24458 ("Trau") is respectfully traversed.

The Office has taken the position that Trau anticipates previously presented claim 32 because Trau discloses, *inter alia*, "a carrier having one or more reporter beads (i.e., includes presently claimed range of 3 to 10 particles per bead) noncovalently attached thereto..." See May 3, 2010 Office Action at pp. 12-13. Indeed, the Office has admitted that "the 'preferred embodiments' taught by Trau et al. in Figures 6-8 teach more than 10 particles and only 4 different colors, the disclosure of Trau et al. teach utilization of less than 10 particles and utilization of various fluorophores, etc. (i.e. more than four colors; see pages 17-18)." *Id.* at p. 13.<sup>2</sup>

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<sup>2</sup> Applicants point out here that Trau's text at pp. 17-18 refers to the incorporation of fluorescent dyes into a reporter bead. This aspect of Trau is distinct from the issue of the number of reporter beads per carrier.

Applicants believe that this position is not well-taken because Trau does not disclose a composition comprising a plurality of different, spatially encoded beads, comprising a polymer matrix and **from 3 to not more than 10 spatially immobilized, individually detectable particles held in the polymer matrix**, wherein each bead has a diameter of from 0.5 millimeter to less than 2.0 millimeter wherein the diameter of the particles is less than 30 micrometer, the particles being disposed in a spatial configuration relative to one another that constitutes the code serving to identify each bead. Nowhere does Trau require a minimum of three or a maximum of 10 particles per bead. Therefore Trau does not meet this limitation of the claim and accordingly cannot anticipate the claim.

At the outset, the Applicants wish to direct the Examiner's attention to MPEP 2131.03(II), which reads in part(emphasis added):

When the prior art discloses a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with **"sufficient specificity to constitute an anticipation under the statute."** What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, and the reference teaches a broad range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. See, e.g., *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) wherein the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. Further, while there was a slight overlap between the reference's preferred range (150-350 degrees C) and the claimed range, that overlap was not sufficient for anticipation. "[T]he disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." *Id.* at 1000, 78 USPQ2d at 1424. **Any evidence of unexpected results within the narrow range may also render the claims unobvious.**

Stated another way, a broadly disclosed range ("one or more reporter beads") does not anticipate a much narrower range ("from 3 to not more than 10 spatially immobilized, individually detectable particles") when the narrower range is not disclosed with sufficient specificity. Here, the Office has not shown how one of ordinary skill would

read Trau and ascertain with sufficient specificity that "one or more reporter beads" includes and in fact requires "from 3 to not more than 10 spatially immobilized, individually detectable particles."

In the Amendment filed February 17, 2010, Applicants provided a detailed explanation why Trau did not anticipate previously presented claim 32. In order to simplify the issues for consideration, the Applicants wish to focus on one reason, i.e., the number of from 3 to not more than 10 spatially immobilized, individually detectable particles held in the polymer matrix (hereafter "the particle aspect"). This is done without concession as to the existence of other grounds for lack of anticipation.

Trau discloses "[a]n assembly of a carrier having one or more reporter beads non-covalently attached thereto." Trau at Abstract, p. 6, lines 23-24.<sup>3</sup> Trau does not disclose a particular range of reporter beads adhered to the carrier.

The Applicants have previously directed the Examiner's attention to the schematic diagrams shown in Figs. 6-8 and to certain exemplified embodiments and provided reasons why Trau does not disclose a carrier containing from 3 to not more than 10 reporter beads. See February 17, 2010 Amendment at pp. 30-32. As to this aspect, the Office has admitted this to be true. See May 3, 2010 Office Action at page 13.

Applicants would also like to direct the Examiner's attention to the disclosure of Trau at p. 20, lines 22-28, when read in view of Fig. 4. For convenience, this information is reproduced below:

FIG. 4 is an illustrative example of reporter beads attached to a carrier particle wherein there is shown an optical microscope image of three 0.9 um silica reporter beads attached to a 2.5 um silica carrier bead. In this case, attachment was achieved by dissolving NaCl to a mixed aqueous suspension of these particles. The size of reporter beads would typically be much smaller than that of the carrier bead. The image is simply an illustrative example

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<sup>3</sup> For ease of reference, Trau's "carrier" and "reporter beads" should be compared to the claim 32 expressions "polymer matrix" and "particles," respectively.

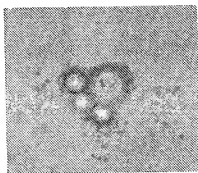


FIG. 4

It is clear from this passage that Trau discloses a 2.5  $\mu\text{m}$  silica carrier bead that contains three 0.9  $\mu\text{m}$  silica reporter beads. Despite this additional information, Applicants believe that the disclosure of Trau does not disclose the particle aspect with sufficient specificity. Nowhere in Trau is it **required** to have the presently claimed particle aspect. By the reference's admission, Figure 4 is just an illustration and no requirement or teaching can be ascribed to it. Even the sizes of the particles relative to the bead are not realistic. Therefore, for at least this reason alone, Trau does not anticipate pending claim 32. (Additionally, the particles on the surface of the bead of Fig. 4 of Trau cannot serve to identify the bead. They would eclipse each other and would not serve as a code to identify the bead.

The Applicants further believe that claim 32 is nonobvious over the disclosure of Trau. Based on the above, Trau does not disclose the presently claimed particle aspect. Furthermore, there is nothing in Trau to suggest to one of ordinary skill that the particle number range (and individual identifiability of each particle) within a bead is critical for identifying the beads of the invention.

The Applicants previously explained the criticality of the particle aspect by directing the Examiner's attention to the "correspondence problem" as described in the specification at pp. 23-25 when read in view of Fig. 11. See February 17, 2010 Amendment at pp. 41-43.

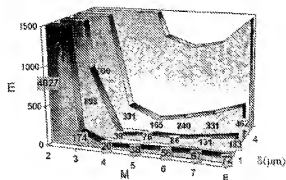
In the May 3, 2010 Office Action, the Office stated at page 4 that:

Applicants contend that the species of particle number per bead is an important limitation in distinguishing the art of record and because of "correspondence problems" (see pages 23-25 of the present specification).

This is not found persuasive because the correspondence problems are related to the method of utilizing the beads and not the structure of the beads.

Applicants respectfully disagree.

For convenience, Fig. 11, in part, is reproduced below.



The specification at pp. 23-24 describes in greater detail aspects of Fig. 11 related to the correspondence problem. Specifically, the specification at p. 20 discloses that "when encoded beads are viewed from two orthogonal angles corresponding to an x,z-projection and a y,z-projection, a 'correspondance problem' arises when two or more spatially immobilised particles have the same z-value..." See, e.g., Fig. 9. Turning to Fig. 11, reproduced in part above, the graph represents a three-dimensional plot of E (the number of ill-identified spatially encoded beads) as a function of M (the number of spatially immobilized particles per encoded bead) and  $\delta$  (in  $\mu\text{m}$ , the standard deviation of the error of the spatially immobilized particle positions). There, it can be seen that for a  $\delta$  value of 1  $\mu\text{m}$ , the number of ill-identified spatially encodes beads (E) varies from 174 ( $M = 3$ ) to 72 ( $M = 8$ ). This should be contrasted to the value of E (4827) when  $M = 2$ . This information supports the criticality of the claimed particle aspect, and not, per se, "the method of utilizing the beads." In other words, *it is a property of the bead, i.e., of the composition, that it is identifiable and not of its intended use.*

The Applicants provide the following additional explanation related to the correspondence problem. When a spatially encoded bead of claim 32 is imaged from two angles a correspondence problem may occur between two or more particles as described

above. When a correspondence problem occurs the relative three-dimensional positions of the particles involved in the correspondence problem cannot be unambiguously determined on the basis of the pair of images. When the correspondence problem occurs between two particles, the images give rise to two possible sets of three-dimensional particle positions. In short, the detection system cannot tell these particles apart. The one such set of particle positions represents the true set of three-dimensional particle positions, whereas the other set of particle positions does not reflect the true set of particle positions. Unfortunately, there is no way to determine which set is true and which is false. Consequently, both sets of particle positions must be stored for the encoded bead being imaged. This ambiguity gives rise to an increased risk of erroneous identification of the bead. When the correspondence problem occurs between more than two particles the images give rise to more than two possible sets of three-dimensional particle positions. As a result the risk of erroneous identification increases even more than is the case when the correspondence problem occurs between only two particles. The probability that a correspondence problem will occur between two or more particles depends on a number of factors – the number of particles being the factor with highest impact. The probability of a correspondence problem increases with the number of particles. On this basis, one would expect that the lower the number of particles the lower the risk of erroneous identification. There is, however, an opposing effect of lowering the number of particles, namely that the number of inter particle distances and angles decreases resulting in a lower number of different possible codes. In other words, at very low numbers of particles per bead there is little risk of a correspondence problem occurring, but the number of different possible codes is very low resulting in an overall high risk of erroneous identification. At the other extreme, i.e. very high number of particles the number of different possible codes is enormous but the frequency of correspondence problems increases dramatically leading to an overall high risk of erroneous identification. As the computer simulations presented in the patent application show there exists an intermediate range of number of particles per bead where the risk of erroneous identification is relatively low. In Fig. 11 this is illustrated by plotting the number of erroneous bead identifications (E) in a set of 5000 encoded beads as a function of the number of particles per bead (M). It can be seen that the number of erroneous



identifications has a local minimum at 4 particles per bead, and that the number increases moderately as the number of particles per bead is increased to 8. On this basis we conclude that the number of particles per bead should be in the range 4 to 8, and that the number of particles per bead should not exceed 10.

The determination of three-dimensional particle positions from a set of orthogonal images is encumbered with some experimental uncertainty. This uncertainty can be expressed as a distance measured e.g. in micrometers. In addition to showing how the number of erroneous bead identifications varies with the number of particles per bead, Fig. 11 also shows how the number of erroneous bead identifications varies with the experimental uncertainty (measured in micrometers) related to determining the particle positions. Not surprisingly, it can be seen that the number of erroneous particle identifications increases with increasing uncertainty of the particle position determination.

One of ordinary skill would not expect, based on the disclosure of Trau, that this correspondence problem exists and that the solution to this problem may be realized by limiting the number of particles "from 3 to not more than 10," as claimed. Trau does not address the same problem as the present invention.

During the November 2, 2010 discussion, the Examiner noted that the data in Fig. 11 are limited to a number of particles ranging from 3 to 8 and thereby suggesting that the showing of criticality (3 to 8) was not commensurate with the recited claim limitation (3 to 10). The examiner does not dispute that the range 3 to 10 is disclosed but rather that the entire range has not been tested.

Applicants direct the Examiner's attention to MPEP 2145, which addresses the Office's Guidelines related to Applicants' rebuttal arguments. There, it is stated in part, with emphasis added, that:

When considering whether proffered evidence is commensurate in scope with the claimed invention, **Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition.** See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a prima facie case of obviousness. *Id.*

For example, a **showing of unexpected results** for a single member of a claimed subgenus, or **a narrow portion of a claimed range would be sufficient to rebut a prima facie case of obviousness if a skilled artisan "could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof."** *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof.).

Here, the Applicants have shown criticality over a large 75% of the claimed range, as opposed to a "narrow portion of the claimed range." Furthermore, the Applicants believe that one of ordinary skill would recognize that the showing of criticality here extends over the entire range of the claimed particle aspect.

Therefore, in view of the fact that Trau does not disclose the claimed particle aspect and does not provide an expectation that the particle aspect is a critical feature, the Applicants believe that the composition of claim 32 is unobvious over Trau. Applicants respectfully request that the Examiner acknowledge the same.

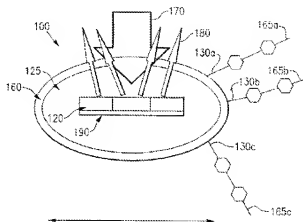
#### **4) The Rejections under 35 U.S.C. § 103(a)**

##### **a) The rejection of claims 2-3, 7-12, 17-20, 24-26, 32-40, 42, and 106-111 under 35 U.S.C. § 103(a) over Trau in view of U.S. Patent No. 6,506,342 ("Frankel") is respectfully traversed**

Applicants provide reasons why Trau fails to render the particle aspect of claim 32 obvious. Applicants believe that Frankel does nothing to cure Trau's deficiency. Indeed, the Office may have implicitly acknowledged that Frankel does not rectify the deficient disclosure of Trau because the Office has relied on Frankel only for its disclosure of the number of bead libraries. See May 3, 2010 Office Action at page 15.

Frankel is generally directed to a "combinatorial chemistry bead that includes an electromagnetic spectral emitter that radiates a distinct electromagnetic code for each bead that uniquely identifies each bead." Frankel, at Abstract. Frankel discloses that an "object of this invention is to provide a distinct ID tag for each bead." *Id.* at col. 6, ll. 44-45. Referring to Fig. 1A, Frankel explains that "the bead 100 includes an ID tag 120 that

is surrounded by a protective encapsulant 125 and molecular anchoring sites 130a-130c that are attached at a plurality of sites on the growth matrix 160." *Id.* at col. 13, ll. 14-17.



**FIG. 1A**

Frankel also explains that the "bead includes a spectral ID tag comprising an electromagnetic spectrum emitter." *Id.* at col. 12, ll. 64-65. Based on this passage, it can be inferred that the ID tag comprises a number of electromagnetic spectrum emitters. Turning to this aspect, Frankel further explains that the number of combinatorial tagged libraries depends on the number of electromagnetic spectrum emitters. For instance, Frankel discloses that "if 6 out of 30 possible emission frequencies are used to tag each bead, then 593,775 unique identification codes are possible." *Id.* at col. 11, ll. 58-60. It should be noted, however, that, in Frankel, the recited range is not related to the number of particles found in a bead, but instead, is the number of frequency emitters required in order to generate a library of tagged beads. Therefore, like Trau, Frankel fails to disclose the particle aspect of the composition recited in claim 32. Therefore, the combination of Trau and Frankel does not render claim 32 obvious, and the Applicants respectfully request that the Examiner acknowledge the same.

- b) The rejection of claims 7-8, 10-11, 25-26, 32, 38-40, 42, and 106-111 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,015,576 ("Nilsson") is respectfully traversed.**

Nilsson generally discloses macroporous polymeric beads containing cavities that can be "used as ion exchangers in gel filtration processes, in hydrophobic

chromatography or in affinity chromatography, optionally subsequent to derivatizing the particles," or as "microcarriers in the cultivation of anchorage-dependent cells." Nilsson at Abstract. The macroporous beads have "a size of 10 to 500 micrometers," and are comprised of certain natural or synthetic polymers. *Id.* at col. 3, ll. 22-23 and ll. 37-42. In Example 9, Nilsson describes an embodiment where an anchorage-dependent cell (i.e., Vero cells) are grown in culture. *Id.* at col. 6, ll. 40ff. There, Nilsson explains that "each bead has to be provided with a minimum number of cells (usually 5-10 cells/bead) as the cells usually are not transferred the between the beads." *Id.* at col. 6, ll. 57-59.

Nilsson is directed to a macroporous polymeric material containing cavities that can be used as a substrate for anchorage-dependent cells. Applicants believe that Nilsson's cells are unrelated to the detectable particles of the composition of claim 32. It may be true that Nilsson's Example 9 describes a bead that contains "a minimum number of cells (usually 5-10 cells/bead)," but Nilsson's beads are not encoded with a code that serves to identify each bead.

Furthermore, Nilsson's use of a minimum number of cells relates to the problem of reducing the initial cell loading on the macroporous polymer bead and, yet again, not to bead identifiability. Nilsson at col. 6, ll. 60-62. The Applicants recited requirement of "from 3 to not more than 10 spatially immobilized, individually detectable particles held in the polymer matrix" is directed to minimizing the correspondence problem related to the code of the encoded bead.

Therefore, the Applicants believe that Nilsson does not render claim 32 obvious at least for the reasons provided above. Acknowledgment of the same is respectfully requested.

#### **IV. Information Disclosure Statement**

Applicants have concurrently filed an Information Disclosure Statement with the present response. Applicants respectfully request that the Examiner consider the cited references. Applicants also request that in the next Office communication, the Examiner provide an indication that each one of the cited references has been considered.

#### **V. Conclusion**

Applicants believe that the amended claims are in a condition for allowance.

In the event that the Examiner discovers an informal matter that can be discussed by telephone, the Examiner is invited to contact Applicants' representative in order to expedite prosecution in the present application. No additional fee is believed to be due; however, the Director is hereby authorized to charge any fees that may be required or credit any overpayment to Deposit Account 13-2725.



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